REMARKS

Claims 35-47, 49-53,55-59,61,62 *and* 65-75 are pending. Claims 35, 37, 41, 43, 46, and 47 have been amended. Claims 1-34, 38, 39, 42, 44, 45, and 48-75 have been canceled. New claim 76 has been added. No new matter has been introduced by way of the amendments provided herein, which are supported by the claims as originally filed and by the specification as a whole. Specific support for the amendments can be found, for example at page 1, lines 9-12; page 6, lines 6-7 and 17-18; page 10, lines 1-7; page 11, lines 3-5; and page 12, lines 20-22. As such, reconsideration of the pending claims in view of the amendments and remarks provided herein is respectfully requested.

Restriction Requirement

Applicant respectfully disagrees with the Examiner and the positions taken with respect to the claimed subject matter. Nevertheless, without acquiescing to the Examiner on these issues, the allegedly non-elected subject matter has been canceled. Applicant reserves the right to pursue the subject matter of these claims in a subsequent application.

Information Disclosure Statement

Applicant thanks the Examiner for considering the references provided in the Information Disclosure Statement of April 18, 2006.

Objections to Specification and Claims

The Examiner objected to the specification and to claim 46. The specification has been amended to delete the allegedly browser-executable code. Claim 46 has been amended to depend from claim 35. In view of these amendments, the objections should be withdrawn.

Biological Deposit Information

Claim 46 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of ordinary skill in the relevant art to make and use the invention. The Examiner has required that the microorganisms recited in the claims be deposited and made publically available. Applicant

respectfully disagrees with the present rejection. However, solely to advance the prosecution of the present case, copies of the deposit receipts for the cell lines of interest are provided. Additionally, during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request; all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application; the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and the deposits will be replaced if they should become nonviable or non-replicable. As can be seen from the deposit receipts, the samples provided have been determined to be viable.

Because the documentation and statements provided herein satisfy the requirements set out in 37 CFR 1.801-1.809, the present rejection should be withdrawn.

The Pending Claims are Adequately Supported

Claim 35-37, 40, 41, 43, 46, and 47 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the written description requirement. Specifically, the Examiner took issue with the proviso language of claim 35 as well as the recitation of bacteriophage variants. This language has been deleted or clarified. As such, the present rejection is moot and should be withdrawn.

Claim 35 has been amended to recite administration of one or more bacteriophages that target, kill, and replicate in *Pseudomonas aeruginosa* in the recited biofilm. Thus, any bacteriophage may be employed in the presently claimed methods that have these easily testable characteristics. Such tests are described in the specification, for example, on page 10, lines 20-31.

The Examiner is also incorrect to imply that the disclosures in the specification are limited to a "panel" of different bacteriophage. The administration of a panel of different bacteriophage is merely one (preferred) aspect of the present invention, as exemplified in Example IV of the present specification. In this regard, a single panel containing multiple different types of *P. aeruginosa* bacteriophage can conveniently be used to treat a wide range of different medical conditions (ie. other than ear infections).

Applicant also notes that a panel of different bacteriophage strains is not always required. As confirmed in the present specification on page 6, lines 23-24, and page 13, lines 2-3, bacteriophage may be used individually. Furthermore, Example II (e) of the present specification, which successfully employs a single bacteriophage strain, for treatment of a *P. aeruginosa* infection of a human burn. Applicant also refer to the results illustrated in Figures 2-3 of the present application (showing the effect of individual bacteriophage strains on *P. aeruginosa).* This treatment is also described the enclosed publication by Marza *et at.* (2006) - see "Case report 1" spanning pages 644-645, which describes administration of a single strain of bacteriophage (and separate sequential administration of antibiotic) to treat a *P. aeruginosa* infection of a human skin burn. A copy of the reference is provided for your reference.

As such, one of ordinary skill in the relevant art would readily recognize that Applicant was in possession of the claimed subject matter at the time the application was filed. As such, the present rejection should be withdrawn.

Claims 46 and 47 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). The Examiner appears to object to a number of elements in the claims. Each is addressed below.

The Examiner appears to take issue with prophylactic aspect of the previously pending claims. The pending claims are now directed to a method of treating a bacterial infection. The treatment focus of the claims addresses the Examiner's concern, thus rendering this portion of the rejection concern moot.

The Examiner also appears to allege that any bacteriophage can be used with the claimed method. The pending claims, as explained above, recite the use of bacteriophages that target, kill, and replicate in *Pseudomonas aeruginosa* present in the biofilm.

The scope of the pending claims was challenged because they were read to encompass treatment of an infection by any bacteria. The current claims are now directed toward *Pseudomonas aeruginosa*. As such, concern over the scope of the claims is now moot. Furthermore, the present Applicant has received confirmation from the FDA and EMEA that the Applicant's data are acceptable to support Phase III clinical trials (*ie*. in humans). This data confirms that - based on the data presented in the specification as filed - a skilled person would be able to treat *P. aeruginosa* infections in humans.

In more detail, the EMEA has reviewed the evidence presented the enclosed papers by Marza *et al.* (2006), and by Wright *et al.* (2009), and confirmed that the Applicant's "BioPhage PA" therapy has no adverse effects and could support entry into Phase III clinical trials in topical indications other than chronic ear and mastoid cavity infections - *eg*. for treating infections associated with, for example, burns and leg ulcers.

The FDA has also reviewed the enclosed Marza *et al.* and Wright *et al.* papers, and confirmed that the Applicant's data are adequate to support the intended Phase III clinical trial.

Hence, based on the disclosures in the specification as filed (as corroborated by the Marza *et al.* and Wright *et al.* papers) a skilled person would be able to put the presently claimed invention into effect without undue experimental burden. As such, the present rejection should be withdrawn.

The Pending Claims are Novel

Claim 35-37, 40, and 43 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Slopek et al. (Archivum Immunologiae Et Therapiae Experimentals, 1984; 32(3): 317-35).

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "It is hornbook law that anticipation must be found in a single reference, device, or process." *Studiengesellschaft Kohle, m.b.H. v. Dart Industries, Inc.*, 726 F.2d 724, 727-728 (Fed. Cir. 1984). There can be no difference between the claimed invention and the cited reference disclosure, as viewed by a person of ordinary skill in the field of the invention, for there to be anticipation. *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

Here, the pending claims recite methods for treating a bacterial infection comprising *P. aeruginosa* infection. Furthermore, the pending claims recite that one or more antibiotics are administered subsequently to the administration of the bacteriophage, and "after the bacteriophage have commenced replication in a targeted *P. aeruginosa* present in the biofilm".

The cited reference fails to disclose these method steps. Because the cited art fails to disclose each and every limitation of the claimed invention, the present rejection should be withdrawn.

The Pending Claims are Nonobvious

Claim 35-37, 40, and 43 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatenable over Slopek *et al.*

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). Second, there must be a reasonable expectation of success found in

the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Third, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

One of ordinary skill in the art would not have been motivated to modify the teachings of Slopek *et al.* to achieve the claimed invention. The cited reference focuses primarily on *Staphylococcal* infection. Referring to Section 14, out of 25 monoinfections, 24 were caused by pyogenic *Staphylococci* and only 1 was caused by *Pseudomonas*. Accordingly, based on Slopek et al., a skilled person would not seriously consider a *P. aeruginosa*-specific therapy, because this would have no significant effect against all but 1 out of 25 skin infections described in "Category XII, Section 1of Slopek *et al.* (and no apparent effect in any of the other "Category XII" skin diseases listed in Sections 13 and 15 of Slopek *et al.*). Based on this limited disclosure, one of ordinary skill in the art would not have been motivated to redirect the teachings of the reference toward a *P. aeruginosa*-specific therapy.

One of ordinary skill in the art would similarly not have a reasonable expectation of success in achieving the claimed invention based on the disclosure of the cited reference. As herein amended, the pending claims recite a "2-step" therapy for bacterial infection comprising *P. aeruginosa* infection. The first paragraph on page 320 of Slopek *et al.* states that therapeutic efficacy was improved when bacteriophage were administered alone, without antibiotics (as compared with the results obtained when bacteriophage and antibiotics were administered in parallel). Furthermore, page 330 of Slopek *et al.* (Section 14) reports that antibiotics were ineffective for treating *Pseudomonas* infection.

Hence, Slopek *et al.* creates a prejudice that would have led a skilled person away from the use of an antibiotic in combination with a bacteriophage. A skilled person reading Slopek *et al.* would have seen no therapeutic advantage to administering any antibiotic in addition to a bacteriophage, and would have had no motivation to do so. In particular, a skilled person reading Slopek *et al.* would not have employed the presently claimed "2-step" protocol for administration of bacteriophages followed by antibiotics.

Lastly, as discussed above, the cited reference fails to teach or suggest all the limitations of the claimed invention. The pending claims recite a 2-step therapy. In contrast, the method described in Slopek *et al.* employs bacteriophage alone, or parallel administration of bacteriophage

and antibiotics (ie. the bacteriophage and antibiotics are administered at the same time) - see Slopek *et al.* page 318, lines 9-10, and page 320, first paragraph.

Slopek *et al.* fails to appreciate the importance of delaying antibiotic administration until after the bacteriophage have commenced replication in a targeted *P. aeruginosa* present in the biofilm. As such, the identification that the timing of antibiotic administration has an effect on therapeutic efficacy is entirely unexpected in view of Slopek *et al.*

In this regard, as discussed in the present specification (see page 2, lines 24 to page 4, line 27) biofilms are notoriously difficult to penetrate. As such, bacterial infections associated with biofilms are resistant to antibiotics, and administration of an antibiotic at the same time as a bacteriophage typically results in no observable antibiotic effect.

In contrast, studies conducted by the present Applicant have surprisingly identified that initial administration of a bacteriophage allows the bacteriophage to start breaking down the biofilm, thereby making the biofilm more accessible for antibiotics to penetrate and destroy the bacteria present within the biofilm.

This unexpected technical effect is evidenced by Example IV of the present specification (see pages 40-41), which describes treatment of *P. aeruginosa* ear infections in two dogs. The dogs were initially treated with bacteriophages and subsequently (8 days or 4 days later, following replication of the bacteriophages in the targeted *P. aeruginosa*) the dogs were treated with antibiotics. In each case, the dogs' clinical symptoms resolved completely.

As reported in the "Result" section of each "Case" in Example IV, the administration of antibiotics after administration of bacteriophages was efficient in treating the infection (as compared with the use of antibiotics alone, or other treatments, which did not clear the infection).

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 255352001900. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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